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Pharmacokinetics of Intravenous Recombinant Human Granulocyte Colony-Stimulating Factor (rhG-CSF) in Children Receiving Myelosuppressive Cancer Chemotherapy: Clearance Increases in Relation to Absolute Neutrophil Count With Repeated Dosing

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Limited evidence suggests increased efficacy of rhG-CSF by subcutaneous (SQ) compared with intravenous (IV) administration. To examine the possibility that rapid elimination of IV rhG-CSF could substantially shorten the duration of systemic exposure and could explain a difference in pharmacodynamics, we characterized the pharmacokinetic profile of IV rhG-CSF for comparison to that previously reported for SQ administration. Twelve children were randomly assigned to receive 10 or more days of IV rhG-CSF at dosages of 5 or 10 μg/kg a day beginning 24 hr after chemotherapy. Enzyme-linked immunosorbent assay (ELISA) was used to measure rhG-CSF concentrations in timed serum samples on days 1 and 10. Pharmacokinetic parameters were estimated by nonlinear, least squares regression. All serum concentration-time profiles were best described by a two-compartment model of elimination. Mean $t_{1/2\beta}$ values ranged from 3.68 ± 0.86 to 22.4 ± 12.0 hr. ANC was correlated with log CL_T ($r = 0.72, P < 0.05$), and inversely with log dose-adjusted AUC ($r = -0.75, P < 0.05$) and log dose-adjusted C_{max} ($r = -0.65, P < 0.05$). Estimated duration of serum rhG-CSF concentrations above 1 ng/ml exceeded 24 hr for all but the 5 μg/kg cohort on day 1. Pharmacokinetic parameters of IV rhG-CSF are similar to those previously reported for SQ administration in children treated with myelosuppressive cancer chemotherapy. Daily IV administration should be a suitable alternative route of administration in this patient population. Am. J. Hematol. 54:124–130, 1997

Key words: recombinant human granulocyte colony-stimulating factor; pharmacokinetics; neutrophils

INTRODUCTION

Bone-marrow suppression is the major dose-limiting toxicity associated with cancer chemotherapy, often requiring dosage reduction or treatment delay. The duration of neutropenia, generally defined as an absolute neutrophil count (ANC) <1,000 cells/μl, is directly related to the risk of infection [1]. Recombinant human granulocyte colony-stimulating factor (rhG-CSF; filgrastim; Neupogen®, Amgen, Inc., Thousand Oaks, CA), is approved for the prevention of febrile neutropenia in patients with nonmyeloid malignancy who have received myelosup-

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pressive chemotherapy [2]. rhG-CSF supports host defenses by stimulating the proliferation and differentiation of neutrophil progenitor cells and the activation of mature neutrophil functions, such as enhancement of phagocytic activity and antibody-dependent cellular cytotoxicity [3]. rhG-CSF decreases the incidence of febrile neutropenia, documented infections, mucositis, and the number and duration of hospital admissions related to febrile neutropenia or documented infections [4].

rhG-CSF is approved for administration by either the intravenous (IV) or subcutaneous (SQ) route. However, limited evidence from adult studies suggests that SQ administration of rhG-CSF is associated with prolonged serum concentrations and a heightened hematopoietic response in comparison to IV administration [5,6]. A recent randomized, crossover study in 8 adult patients with acute myelogenous leukemia (AML) comparing rhG-CSF administered by continuous SQ infusion at a reduced dose (33 $\mu g/m^2$ a day) to IV infusions of a standard rhG-CSF dose (200 $\mu g/m^2$ a day) showed no difference in hematologic or clinical parameters between the two routes of administration [7].

Patients receiving cancer chemotherapy frequently have permanent central venous catheters. Nevertheless, rhG-CSF is most often administered by SQ injection because it is presumed that SQ administration results in a longer duration of systemic exposure and heightened hematopoietic response. IV administration would lessen the discomfort and anxiety experienced by patients (especially children) who receive daily injections of rhG-CSF.

The pharmacokinetic profiles of both IV and SQ rhG-CSF are well-established in adult patients [8–13]. Although the pharmacokinetic profile of SQ rhG-CSF has been well-characterized in children, little has been published about the disposition of rhG-CSF when administered by the IV route [14–16]. The main objectives of this study were to characterize the single and multiple-dose pharmacokinetic profiles of IV rhG-CSF in children receiving myelosuppressive cancer chemotherapy for comparison to published pharmacokinetic parameters for SQ rhG-CSF. In addition, since the duration of exposure to effective levels of rhG-CSF may be an important determinant of hematopoietic response, we estimated the durations of rhG-CSF serum concentrations above the estimated concentration required for half-maximal biologic activity (EC_{50}) of 0.3 ng/ml [17–19].

MATERIALS AND METHODS

Subjects

This study involved 12 children, ages 2–18 years, who were undergoing myelosuppressive chemotherapy for treatment of nonmyeloid malignancy at Robert Wood Johnson University Hospital (Table I). All subjects had normal hepatic, renal, and cardiac function. Exclusion criteria included a history of central nervous system metastases, or bone-marrow transplantation. The study was approved by the Institutional Review Board of UMDNJ-Robert Wood Johnson Medical School, with written informed parental consent obtained for all subjects prior to study participation.

Study Design

Subjects were randomized to receive rhG-CSF at a dose of 5 or 10 $\mu g/kg$ by 30 min IV infusion once daily for a minimum of 10 days, beginning at least 1 day after completion of the most recent chemotherapy cycle. Timed venous blood samples were obtained for determination of serum rhG-CSF concentration-time profiles on day 1 (single dose) and day 10 (multiple dose) in both dosage cohorts. Safety and tolerability assessments included physical examinations, vital signs, oral temperature, and laboratory safety tests. ANC values were calculated on days 1 and 10 of rhG-CSF administration. Differentials were not available for subjects with total white blood cell counts of $<$1,000 cells/μl.

Analytic Methods

Serum rhG-CSF concentrations were estimated by a sandwich enzyme-linked immunosorbent assay (ELISA) method (Quantikine Human G-CSF Immunoassay®, R & D Systems, Inc., Minneapolis, MN), which utilized a murine monoclonal anti-rhG-CSF capture antibody and polyclonal rabbit anti-rhG-CSF reporter antibody coupled to streptavidin-horseradish peroxidase for spectrophotometric estimation of rhG-CSF concentrations [20].

Pharmacokinetic Analysis

The pharmacokinetic parameters area under the serum concentration vs. time curve (AUC), maximum serum concentration (C_{max}), apparent volume of distribution at steady state (V_{ss}), distribution half-life ($t_{1/2\alpha}$), terminal elimination half-life ($t_{1/2\beta}$), and total body clearance (CL_T) were estimated from serum concentration vs. time data utilizing nonlinear least squares regression with PCNONLIN 4.2 (SCI Software, Apex, NC). The weighted factor in all calculations was the inverse of the square of each serum concentration. The AUC from time zero to the last measurable concentration (24 hr) was calculated by the linear trapezoidal rule, with extrapolation to time infinity obtained by adding this value to the last measurable concentration divided by β (the elimination rate constant obtained from the terminal disposition slope of the serum concentration vs. time curve). V_{ss} was calculated from the product $[V_c\ (1 + K_{12}/K_{21})]$, where V_c represented the volume of distribution of the central compartment, K_{12} the rate constant describing the movement of rhG-CSF from the central compartment to the peripheral compartment, and K_{21} the rate constant describing the movement of rhG-CSF from the peripheral compartment to the cen-

TABLE I. Patient Characteristics*

	Study no.	Age (years)	Gender	Diagnosis	Prior chemotherapy agents	Prior therapy (months)	Baseline ANC (cells/μl)
5 μg/kg	1	12	F	ALL	Asp, VCR, DNR, ARA-C, MTX, Pred, 6-TG, CTX	15.5	n/a
	4	16	F	ALL	Asp, VCR, DNR, ARA-C, MTX, Pred, 6-TG, CTX, 6-MP, DOX, DEX	10.0	n/a
	6	7	F	ALL	Asp, VCR, DNR, ARA-C, Pred, 6-TG, CTX, 6-MP	9.37	1,320
	8	7	M	ALL	Asp, VCR, DNR, Pred, CTX	0.47	5,922
	9	6	F	Rhabdo	Ifos, CBDCA, VP-16, VCR, DOX	0.70	3,072
	11	16	F	ES	Ifos, VP-16	0.70	2,322
Mean ± SEM		10.7 ± 1.89				6.12 ± 2.61	3,159 ± 988
10 μg/kg	2	14	F	SCS	Ifos, CBDCA, VP-16	3.03	1,566
	3	8	M	ALL	Asp, VCR, DNR, ARA-C, Pred, 6-TG, CTX	4.17	n/a
	5	12	F	ALL	Asp, VCR, DNR, MTX, Pred, CTX, 6-MP, DOX, DEX	14.3	n/a
	7	15	M	ALL	Asp, VCR, DNR, ARA-C, Pred, CTX, 6-MP	1.63	n/a
	10	18	M	ALL	Asp, VCR, DNR, ARA-C, Pred, CTX, 6-MP	1.57	1,672
	12	14	M	NHL	VCR, ARA-C, MTX, Pred, CTX, DOX, VP-16	2.30	1,344
Mean ± SEM		13.5 ± 1.36				4.50 ± 2.00	1,527 ± 96.6

*ALL, acute lymphocytic leukemia; Rhabdo, rhabdomyosarcoma; ES, Ewing's sarcoma; SCS, spindle-cell sarcoma; NHL, non-Hodgkin's lymphoma; Asp, asparaginase; VCR, vincristine; DNR, daunorubicin; ARA-C, cytosine arabinoside; MTX, methotrexate; Pred, prednisone; 6-TG, thioguanine; CTX, cyclophosphamide; 6-MP, mercaptopurine; DOX, doxorubicin; DEX, dexamethasone; Ifos, ifosfamide; VP-16, etoposide; CBDCA, carboplatin; n/a, differential not available.

tral compartment. The $t_{1/2\alpha}$ was calculated from the quotient (ln 2/α), with α (the distribution rate constant) calculated from serum concentration vs. time data by the method of residuals. The $t_{1/2\beta}$ was calculated from the quotient (ln 2/β), and CL_T from the quotient (dose/AUC). Duration (in hr) of rhG-CSF serum concentrations >0.1 ng/ml was calculated from the quotient [(ln Cmax − ln 0.1)/β], and duration >1 ng/ml from the quotient [(ln Cmax − ln 1)/β].

Statistical Analysis

Demographic and baseline clinical characteristics were compared with Fisher's exact test for nominal variables, and an unpaired Student's t-test for continuous variables. Intergroup differences in hematologic and pharmacokinetic parameters were compared by the unpaired Student's t-test. The paired Student's t-test was used to compare intrasubject differences between days 1 and 10 within each dosage group. Linear regression was used to analyze the potential correlation between ANC and log transforms of rhG-CSF clearance, dose-adjusted AUC, and dose-adjusted C_{max}. $P < 0.05$ was considered statistically significant for all analyses.

RESULTS

Subjects

A comparison of the clinical and demographic characteristics of the patients in the 5 μg/kg and 10 μg/kg cohorts is presented in Table I. Age, gender, and months of prior chemotherapy were not significantly different between dosage cohorts. In addition, the 5 μg/kg and 10 μg/kg cohorts were well-matched with respect to baseline G-CSF concentration (0.21 ± 0.13 vs. 0.38 ± 0.11 ng/ml, respectively) and baseline ANC (3,159 ± 988 vs. 1,527 ± 96.6 cells/μl, respectively), neither of which differed significantly. A total of 12 subjects was studied. Day 1 and 10 pharmacokinetic parameters in subject 4 (5 μg/kg) were greater than two standard deviations from the respective mean values. This subject was therefore excluded from pharmacokinetic and hematologic evaluations on both study days, with the remaining 11 subjects used to calculate reported mean values.

Single and Multiple-Dose Pharmacokinetic Profile of IV rhG-CSF

Serum rhG-CSF concentration-time profiles were best described in all subjects by a two-compartment model with rapid distribution and prolonged elimination (Fig. 1 and Table II). Among the dosage groups, mean $t_{1/2\alpha}$ (± SEM) ranged from 0.54 ± 0.31 to 0.93 ± 0.39 hr, and $t_{1/2\beta}$ ranged from 3.68 ± 0.86 to 22.4 ± 12.0 hr. C_{max} values ranged from 98.7 ± 18.6 to 197 ± 60.3 ng/ml. Twenty-four-hr serum rhG-CSF concentrations ranged from 0.46 ± 0.15 to 3.58 ± 1.79 ng/ml. The mean V_{ss}

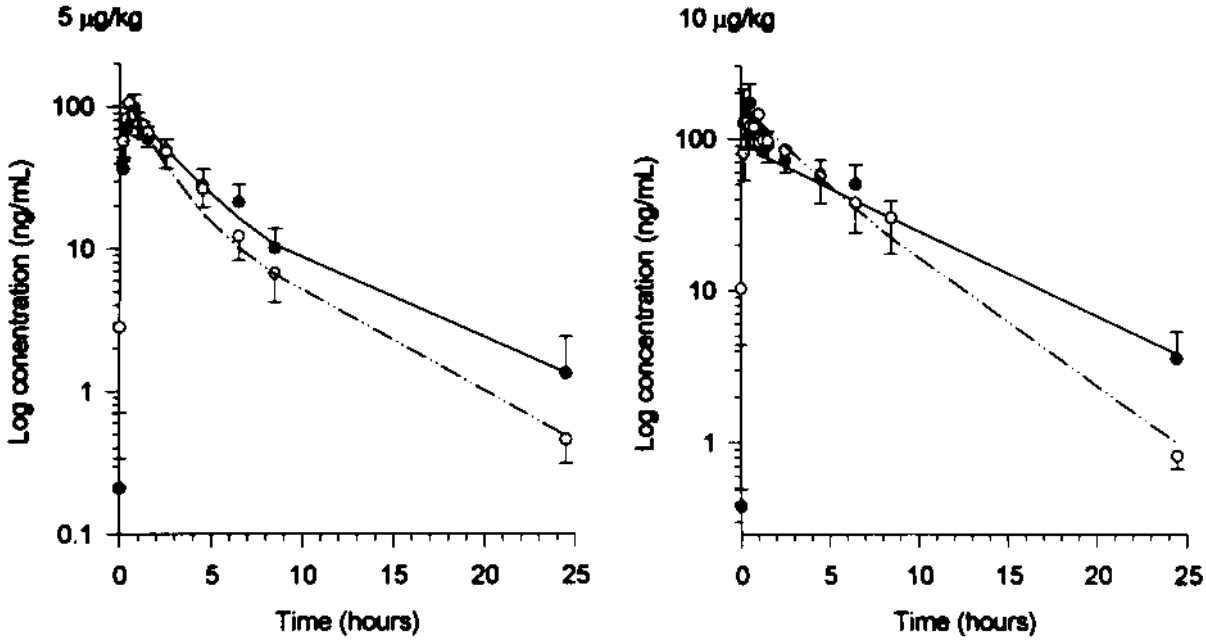

Fig. 1. Single and multiple-dose serum concentrations vs. time of IV rhG-CSF. For both 5 μg/kg and 10 μg/kg recipients, observed mean (±SEM) serum concentrations on day 1 are represented by •, with predicted concentrations represented by ——, while on day 10 observed mean (± SEM) serum concentrations are represented by ○ and predicted concentrations by — · ·.

TABLE II. Comparison of Pharmacokinetic Parameters Between Study Days 1 and 10

Parameter	Mean ± SEM (day 1)	Mean ± SEM (day 10)	Mean ± SEM (day 1)	Mean ± SEM (day 10)
5 μg/kg (n = 5)			10 μg/kg (n = 6)	
AUC (ng per hr/ml)	282 ± 48.7	219 ± 42.3	765 ± 206	631 ± 184
C_{max} (ng/ml)	98.7 ± 18.6	108 ± 12.6	197 ± 60.4	166 ± 41.6
V_{ss} (l/kg)	0.06 ± 0.01	0.14 ± 0.06	0.10 ± 0.03	0.21 ± 0.13
$t_{1/2\alpha}$ (hr)	0.81 ± 0.26	0.87 ± 0.30	0.54 ± 0.31	0.93 ± 0.39
$t_{1/2\beta}$ (hr)	3.68 ± 0.86	22.4 ± 11.9	4.47 ± 0.68	11.7 ± 5.63
CLT [l/(kg per hr)]	0.02 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.07 ± 0.04

ranged from 0.06 ± 0.01 to 0.21 ± 0.13 l/kg. Mean AUC and C_{max} were higher in the 10 μg/kg group than in the 5 μg/kg group, roughly in proportion to dose, although these differences were not statistically significant. There were no consistent dose-related differences in V_{ss}, $t_{1/2\alpha}$, $t_{1/2\beta}$, or CL_T.

ANC values were not different between 5 μg/kg or 10 μg/kg recipients immediately prior to rhG-CSF treatment (day 1); however, mean ANC values were significantly higher in the 10 μg/kg group than the 5 μg/kg group on day 10 (10,377 ± 1,839 vs. 2,966 ± 1,386 cells/μl, $P < 0.05$; Fig. 2).

Some published reports have described a possible association between the ANC and the elimination of circulating G-CSF, thought to be mediated by internalization and degradation of receptor-bound G-CSF in granulocytes [14,16]. In the present study, we found a significant positive correlation between ANC and log CL_T among all evaluable subjects ($r = 0.72$, $P < 0.01$; Fig. 3). Accordingly, we also observed significant negative correlations between ANC and log dose-adjusted AUC ($r = -0.75$, $P < 0.01$; Fig. 4) and between ANC and log dose-adjusted C_{max} ($r = 0.65$, $P < 0.05$; Fig. 5).

As shown in Table III, the mean duration of serum rhG-CSF concentration above 1 ng/ml was >24 hr (the dosing interval) in all group samples, except for the 5 μg/kg cohort on day 1 (23.8 ± 5.10 hr).

DISCUSSION

The pharmacokinetic profile of rhG-CSF is well-established in adult patients receiving myelosuppressive cancer chemotherapy, but less is known about the disposition of this agent, particularly by the IV route, in children. In

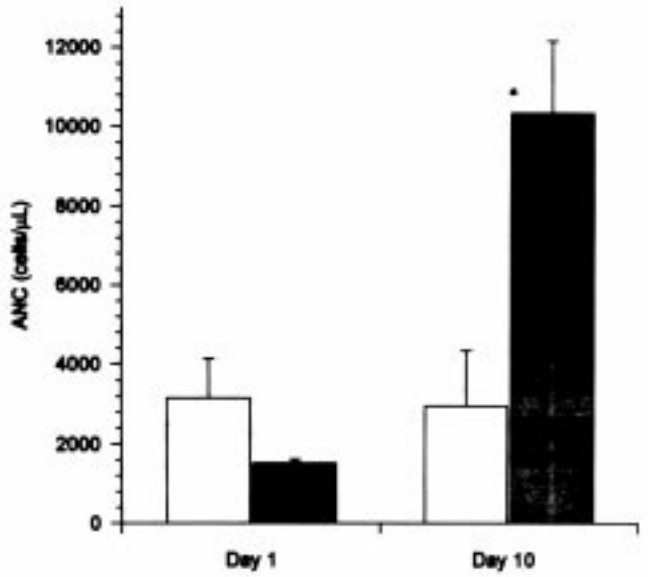

Fig. 2. Comparison of mean ANC values between 5 mg/kg and 10 mg/kg cohorts with IV rhG-CSF administration. Mean (± SEM) ANC values in 5 μg/kg recipients are represented by white columns with values in 10 μg/kg recipients represented by shaded columns. *$P < 0.05$.

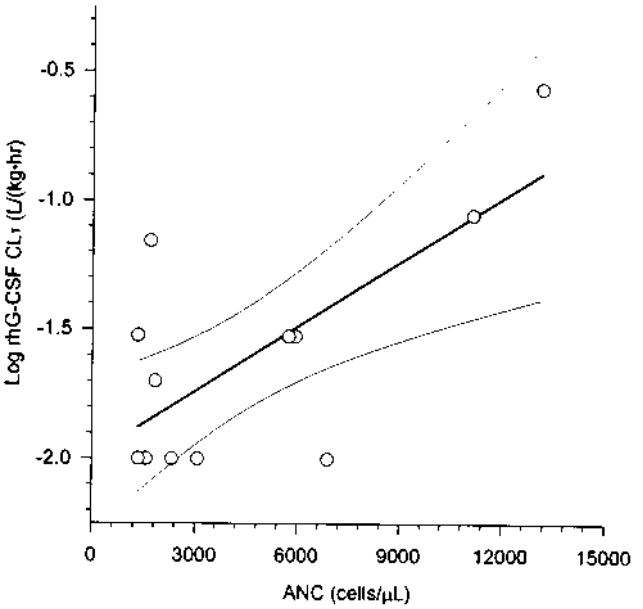

Fig. 3. Correlation between ANC values and log rhG-CSF CLT. ANC values on days 1 and 10, represented by ○, are shown plotted against log total body rhG-CSF CLT values. Regression line ($r = 0.72$, $P < 0.01$) is shown in relation to 95% confidence intervals, and is described by the equation [log rhG-CSF CLT = −1.99 + (0.0000843 × ANC)].

this study, we examined the single and multiple-dose pharmacokinetics of rhG-CSF given by 30-min IV infusion at 5 μg/kg or 10 μg/kg once daily for 10 consecutive days in 12 children following myelosuppressive cancer chemotherapy. The serum G-CSF concentration-time profiles were best described in all subjects by a two-compartment model of elimination, suggesting that rhG-CSF was distributed to both a central (intravascular or well-perfused) and a "peripheral" compartment. Studies of IV rhG-CSF in adult patients have also reported two-compartment disposition, with pharmacokinetic parameters similar to those we report [9,10]. Circulating G-CSF may be eliminated in part through receptor-mediated internalization and degradation [14,16]. The peripheral compartment may represent leukocytes or endothelial cells. The median V_{ss} in our patients was 0.07 l/kg, which indicates that rhG-CSF was not extensively distributed to extravascular tissue compartments. As displayed in Table II, rhG-CSF distribution was rapid, followed by prolonged elimination. The biexponential behavior observed in our study is consistent with rapid binding of rhG-CSF to circulating neutrophils (in the α phase), and a kinetically slower equilibrium between bound and free rhG-CSF in the circulation. In support of this hypothesis, reversible temperature-dependent binding of G-CSF to mature neutrophils in vitro has been demonstrated [18].

In previous studies of SQ rhG-CSF in children, significant increases in rhG-CSF clearance with repeated dosing were attributed to receptor-mediated endocytosis and degradation by increasing numbers of mature circulating neutrophils during therapy [14,16]. Our findings of the significant positive correlation between ANC and log CL_T ($r^2 = 0.35$, $P < 0.05$), and the negative correlation between ANC and the log of the dose-adjusted AUC ($r^2 = 0.41$, $P < 0.05$), were consistent with such a mechanism. Accordingly, mean dose-adjusted AUC was increased and mean CL_T was decreased from day 1 to day 10 in both dose groups; however, high variation in ANC and low sample size precluded demonstrating statistical significance of these associations.

Duration of systemic exposure may be an important factor in determining a drug's pharmacodynamic effect. Specifically, very short duration of exposure could lessen hematopoietic effect of G-CSF independent of C_{max} or AUC. Therefore, we compared the half-lives, the durations of serum G-CSF concentrations above target concentrations of 0.1 ng/ml and 1 ng/ml, and the serum concentrations at 24 hr following IV infusion to those reported following SQ administration of rhG-CSF. In a study of SQ rhG-CSF at doses of 5–15 μg/kg once daily for 10 days in 15 chemotherapy-treated children with advanced neuroblastoma, the mean $t_{1/2\beta}$ was 5.8 ± 2.1 hr on day 1 and 4.5 ± 2.1 hr on day 10. Median 24-hr concentrations on day 10 ranged from 0.1–23.9 ng/ml [14]. Similarly, in a study of SQ rhG-CSF at a dosage of 5 μg/kg/day for 10 days in 56 children with various

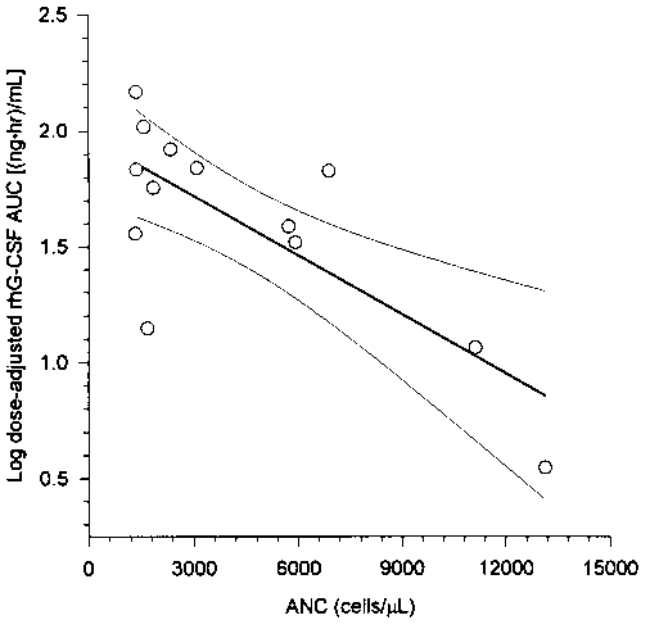

Fig. 4. Correlation between ANC values and log dose-adjusted rhG-CSF AUC. Day 1 and 10 ANC values for each patient are represented by ○, and are shown plotted against log dose-adjusted rhG-CSF AUC values. Regression line ($r = -0.75$, $P < 0.01$) is shown with 95% confidence intervals, and is described by the equation [log dose-adjusted rhG-CSF AUC = 1.98 + (0.0000851 × ANC)].

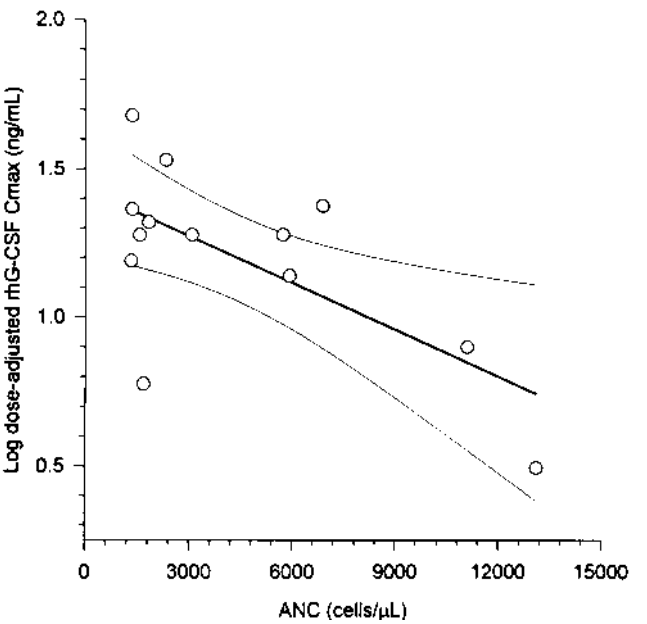

Fig. 5. Correlation between ANC values and log dose-adjusted rhG-CSF C_{max}. Day 1 and 10 ANC values for each patient are represented by ○, and are shown plotted against log dose-adjusted rhG-CSF C_{max} values. The regression line ($r = -0.65$, $P < 0.05$) is shown in relation to 95% confidence intervals, and is described by the equation [log dose-adjusted rhG-CSF C_{max} = 1.43 + (0.0000521 × ANC)].

TABLE III. Estimated Durations of Serum rhG-CSF Concentrations Following IV Administration

		Hr >0.1 ng/ml	Hr >1.0 ng/ml
5 μg/kg (n = 5)			
Mean ± SEM	Day 1	36.0 ± 7.92	23.8 ± 5.10
Mean ± SEM	Day 10	227 ± 121	151 ± 80.9
10 μg/kg (n = 6)			
Mean ± SEM	Day 1	48.7 ± 9.10	33.9 ± 6.90
Mean ± SEM	Day 10	112 ± 50.2	73.5 ± 31.8

malignancies, the mean $t_{1/2\beta}$ on the first dosing day was 8.4 ± 0.6 hr [15]. Our results are comparable to those of both prior studies: the mean day 1 and day 10 $t_{1/2\beta}$ values at the 5 μg/kg and 10 μg/kg doses were 3.68 ± 0.86, 22.4 ± 12.0, 4.47 ± 0.68, and 11.7 ± 5.64 hr, respectively, while the respective mean 24-hr serum concentrations were 1.34 ± 1.20, 0.46 ± 0.15, 3.58 ± 1.79, and 0.82 ± 0.37 ng/ml.

On the assumption that the EC_{50} of rhG-CSF on human neutrophils is 0.3 ng/ml, we utilized the $t_{1/2\beta}$ values derived in our patients to estimate the durations for which serum rhG-CSF concentrations would remain above 0.1 and 1 ng/ml [21]. As shown in Table III, mean durations approximated or exceeded 24 hr in both dosage cohorts, on both days 1 and 10, with the exception of the amount of time above 1 ng/ml (23.8 ± 5.10 hr) in the 5 μg/kg cohort on day 1.

CONCLUSIONS

IV administration of rhG-CSF results in circulating G-CSF levels which are sufficiently prolonged to provide near-continuous exposure to target serum concentrations on a once-daily dosing schedule. Our study design did not permit analysis of treatment efficacy. Further studies are indicated to definitively address the question of comparable hematopoietic efficacy between IV and SQ administration of rhG-CSF. However, on the basis of pharmacokinetic disposition and duration of serum concentrations, IV administration should be considered

a suitable route of rhG-CSF administration in this patient population.

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